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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,912	09/11/2000	Charles A. Vacanti	07917-082002	2934

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,912	VACANTI ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-44* is/are rejected.

7)☒ Claim(s) *41-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 September 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. This application (09/658912) was withdrawn from issue after payment of the issue fee due to unpatentability of one or more claims. See 37 CFR 1.313(b)(3). This application (09/658912) is hereby withdrawn from issue and prosecution on the merits is hereby re-opened.

2. Claims 1-40 and 45-53 are cancelled. Claims 41-44 will be examined to the extent that they read on isolated, mammalian adult autonomic nervous system neural stem cells.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: The full name of each inventor (family name and at least one given name together with any initial) has not been set forth.

Priority

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows: the disclosure for USPT 6027744 is not enabling for isolated adult mammalian neural stem cells.

Title

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

7. The following title is suggested:

ISOLATED MAMMALIAN ADULT AUTONOMIC NERVOUS SYSTEM NEURAL STEM CELLS.

Drawings

8. The drawings are objected to under 37 CFR 1.83(a). The drawings must show every feature of the invention specified in the claims. Therefore, the neural stem cells must be shown or the feature(s) canceled from the claim(s). No new matter should be entered.

9. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

10. The Specification is objected to because of the following informalities: Abstract must be entitled "Abstract" or "Abstract of Disclosure". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 41-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 41 is directed an isolated, mammalian adult autonomic nervous system neural stem cell. Claim 42 is directed to the isolated stem cell of claim 41, wherein the cell is isolated from heart, bladder, intestine, lung, liver, or kidney tissue. Claim 43 is directed to an isolated, mammalian adult neuroendocrine stem cell. Claim 44 is directed to the stem cell of claim 43, wherein said cell is isolated from adrenal gland or pancreas tissue..

12. The specification teaches that stem cells can be isolated from any innervated tissue of the body, including the heart, bladder, intestine, lung, liver, and kidney tissue. In addition, neural stem cell can be isolated from spinal cord tissue, brain tissue, and other central nervous system tissues, as well as from peripheral nervous tissues, autonomic nervous system tissues. Pre-ganglionic autonomic nervous system stem cells are located in the gray matter of the spinal cord and therefore are isolated in the same way as, and in conjunction with, spinal cord stem cells.

13. While general guidance is provided regarding isolation of stem cells from rats, no working examples are provided re: characterization of said cells as neural stem cells, maintenance of said cells in culture, purification of isolated tissue to enrich said culture, or production of a homogenous culture of neural stem cells.

14. The art teaches that the autonomic nervous system has three major divisions: sympathetic, parasympathetic, and enteric. The sympathetic and parasympathetic divisions innervate cardiac muscle, smooth muscle, and glandular tissue and mediate a variety of visceral reflexes. These two divisions include the sensory neurons associated with spinal and cranial

nerves, the pre-ganglionic and post-ganglionic motor neurons, and the central nervous system circuitry that connects with and modulates the sensory and motor neurons. The enteric division has greater autonomy than the other two divisions and comprises a largely self-contained system, with only minimal connections to the rest of the nervous system. It consists of sensory and motor neurons in the gastrointestinal tract that mediate digestive reflexes (Kandel, 2000). Further, stem cells in the post-natal (adult) animal are limited to specific types and regions (e.g. bone marrow pluripotent blood cells or multipotent astrocytes in the subventricular zone). Neural stem cells are especially uncommon and limited in distribution (Weiss et al., 1996). The vast majority of neural cells in adult animals are not stem cells (Taupin & Gage, 2002; Johansson et al., 1999; Palmer et al., 1997).

15. Thus the claimed invention is directed to an isolated mammalian adult autonomic nervous system neural stem cell or an isolated, mammalian adult neuroendocrine stem cell, which is not supported by the teachings of the prior art (Palmer and Gage, 1995; USPT 5411883; USPT 5589376). One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specific cell types which are claimed; From which mammalian species do the neural stem cells originate?; Where in any given mammal neural stem cells would be found; How to identify neural cell; Age of animals necessary to be considered "adult"; Purification of isolated cultures to eliminate non-stem cells; Whether or not dead animals are an acceptable source of neural stem cells; How to identify stem cells; Expectation of success in maintaining a neural stem cell culture. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as

defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and prior art for the following reasons.

16. Regarding the scope of neural stem cells, the art recognizes the enormous range of cells that fall under this category, specifically any cells which are derived from the neural crest. Due to the large quantity of experimentation necessary to all neural stem cells, the lack of direction/guidance presented in the specification regarding study of neural stem cells, the absence of working examples directed to neural stem cells, the complex nature of the invention, the unpredictability of neural stem cells (Zulewski et al., 2001; Schwab, 2002; USPT 5411883; USPT 5589376), and the breadth of the claims which fail to recite limitations which neural stem cells, especially the expected descent cell types, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

17. Regarding the scope of adult stem cells, the art recognizes the few if any stem cells in the adult are present in the nervous system, especially the central nervous system. Due to the large quantity of experimentation necessary to find stem cells in an adult mammal, the lack of direction/guidance presented in the specification regarding characterizing stem cells, the absence of working examples directed to adult stem cells, the complex nature of the invention, the unpredictability of adult stem cells (Palmer and Gage, 1995; USPT 5411883; USPT 5589376), and the breadth of the claims which fail to recite limitations which adult stem cells, especially those originating the nervous system of an adult mammal, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

18. Regarding the scope of "isolated", the art recognizes that any cells dissected out of an animal (in the instant case an adult mammal) and place in tissue culture qualify as "isolated".

Due to the large quantity of experimentation necessary to isolate stem cells from an adult mammal, the lack of direction/guidance presented in the specification regarding isolation of stem cells, the absence of working examples directed to isolation versus purification or homogenization of a culture, the complex nature of the invention, the unpredictability of primary cell culture (USPT 5411883; USPT 5589376), and the breadth of the claims which fail to recite limitations what constitutes "isolation", undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

19. Claims 41-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Emura (1997). Emura (1997) describes the isolation of stem cells from liver, intestine, glandular, and lung tissue (organs). The liver stem cells are multipotent and isolated from adult rats, thus meeting the limitations of claims 41 and 42 (pp. 4). Emura (1997) also notes that some stem cells from the liver can differentiate and become pancreatic bile duct cells thus meeting the limitations of claims 43 and 44 (pp. 4). Emura also teaches multipotent intestine cells isolated from mice thus meeting the limitations of claim 42 (pp. 4). Emura further teaches the isolation and characterization of stem cells from lung tissue of rats, hamsters, and rabbits that have the ability to form endocrine cells thus meeting the limitations of claims 43 and 44 (pp. 5 and Table I).

20. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Gritti et al. (1997). Gritti et al. (1997) teaches the isolation of stem cells from the brains of adult mice. The isolated stem cells are multipotent and self-renewing thus meeting the limitations of claim 41 (pp. 1093-1094).

21. Claims 41 and 43-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Cornelius et al. (1997). Cornelius et al. (1997) teaches the isolation of pluripotent islet-producing stem cells from adult mice. The stem cells are capable of forming islets in vitro that were immunopositive for glucagons, insulin, and somatostatin thus meeting the limitations of claim 43 (pp. 273). The stem cells were isolated from the pancreas of an adult mouse thus meeting the limitations of 41 and 44 (Materials and Methods).

22. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Weiss et al. (1996). Weiss et al. (1996) teaches the isolation of neural stem cells from the lumbar/sacral segment of the spinal cord and the third and fourth ventricles. These cells were isolated from adult mice thus

meeting the limitation of claim 41 (Materials and Methods). In addition, the aforementioned cells are multipotent, self-renewing, and expandable stem cells thus meeting the limitations of claim 41 (Figure 5).

23. Claim 41 is rejected under 35 U.S.C. 102(e) as being anticipated by USPT 5851832 (1998). USPT 5851832 (1998) teaches the isolation of neural stem cells from mammalian tissues. The stem cells are isolated from mammalian tissue (including adults) and multipotent thus meeting the limitations of claim 41 (Col. 12 lines 5-65).

24. Claim 43 is rejected under 35 U.S.C. 102(e) as being anticipated by USPT 5851832 (1998). USPT 5851832 (1998) teaches the isolation of neural stem cells from mammalian tissues. The stem cells can be isolated from the central or peripheral nervous system; this includes "neuroendocrine stem cells" thus meeting the limitations of claim 41 (Col. 13 lines 20-44).

Summary

25. Claims 41-44 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
November 18th, 2002

Gary d Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600